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Franch-Lage, Felicidad; Amigo Rubio, Jose Manuel; Skibsted, Erik; MasPOCH, Santiago; Coello, Jordi

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QUANTITATIVE DETERMINATION OF API AND EXCIPIENTS IN LORAZEPAM TABLETS BY USING NIR-HYPERSPECTRAL IMAGE AND MCR-ALS.

Felicidad Franch-Lage^{1*}, José Manuel Amigo², Erik Skibsted³, Santiago Maspoch¹, Jordi Coello¹

¹Departament de Química, Unitat de Química Analítica, Universitat Autònoma de Barcelona

² Department of Food Science, Quality and Technology. Fac. Life Science, Univ. Copenhagen. Denmark

³Novo Nordisk A/S, Maaloev, Denmark

*felicidad.franch@uab.cat

Abstract

Hyperspectral imaging (especially NIR Imaging) as an analytical tool in pharmaceutical research provides new opportunities to characterize tablets.

Despite the promise of these techniques, there are still some aspects that need to be faced. The main one is the resolution and quantification of analytes at a low concentration in the tablet, particularly in some pharmaceutical formulations, such as antidepressants, where the concentration of Active Principal Ingredient (API) is in very low percentages. A key quality parameter for tablets is to ensure a homogeneous distribution of the API in the tablets.

In this sense, the objective in this presentation is two-fold: to search for a methodology to accurately quantify low-content API formulations and to find procedures to evaluate/quantify the heterogeneity of the API distribution investigated on the surface of the tablet.

With these aims, lorazepam tablets images were analyzed by using augmented Multivariate Curve Resolution (MCR). The obtained results were processed by domain statistics methodologies to assess the uniform distribution of lorazepam in the studied surface.

Keywords - Hyperspectral Imaging, Pharmaceutical dosage forms, Tablets, Lorazepam, MCR-ALS, content uniformity, domain statistics.

INTRODUCTION

The Active Principal Ingredient (API) is present in very low concentrations in some commercial tablets and its distribution depends of many factors (blending process, compactness, cohesive forces, etc). If a tablet needs to be split in half's or the dissolution is affected by API agglomerate sizes, it becomes crucial to assess the correct distribution of API in the tablets (in terms of homogeneity). With the classical techniques like High performance Liquid Chromatography (HPLC), is not possible to obtain information about the distribution of API in each tablet. In order to obtain spatial information of the tablet, hyperspectral Near Infrared (NIR) imaging is being introduced in pharmaceutical research laboratories. This technique allows obtaining information about the distribution of the ingredients from one slice of the tablet, even when they are in very low concentration [1].

Lorazepam is one of the most common prescribed antidepressant drug because of it is fast acting and useful in treating fast onset panic anxiety [2]. This drug has strong sedative and hypnotic effects, and



the duration of clinical effects from a single dose makes it an appropriate choice for the short term treatment of insomnia, particularly in the presence of severe anxiety.

Lorazepam tablets are quite small (0.6 cm of diameter) and have a low concentration of API (around 1%). Sodium Carboximethyl starch (CMS), Magnesium stearate (MgSt), Microcrystalline cellulose (MCC) and Lactose monohydrate (LAC) are the main excipients representing about 99 % of the tablet weight. Prescribed dose of this anxiolytic drug tablets is often the half of the tablet. Therefore, it is highly important to assess the correct and homogeneous distribution of the API and the rest of excipients in the tablet, as the tablets needs to be split in half's by the patients. NIR-CI (Near Infrared-Chemical Image) is an appropriate technique for this issue giving both spatial and quantitative information on the tablet surface.

Augmented MCR (Multivariate Curve Resolution) allows the decomposition of the original data cube into two submatrices [3]. The first submatrix is related to the concentration of each component in the measured surface; whereas the second contains the spectral information

Therefore, the objective of this work is to develop a robust methodology to calculate the percentage of each component in the Lorazepam tablets as well as to study their distribution in the surface to asses the correct homogeneity. The methodology encompasses the measurements with NIR-Chemical imaging and further data analysis by using MCR in the augmented fashion explained in the references[1]] [3]

EXPERIMENTAL

Twelve tablets of Lorazepam (Laboratorios Normon, S.A., Spain) were randomly selected and glued onto a microscope slide. After fixating the tablet surfaces were cut with a microtome to establish a plane surface parallel to the microscope slide. Samples were analyzed on a NIR line mapping system (Spectrum Spotlight 350 FT-NIR Microscope, PerkinElmer, UK) ; 8 scans, were averaged to get the final spectra in the wavelength range 7800–4000cm⁻¹ and 16cm⁻¹ spectral resolution.. An area of 4mm×4mm was analysed using a pixel size of 25 µm×25µm. Each spectrum was measured from wavelength region 7800–4000cm⁻¹ using 16cm⁻¹ spectral resolution. Standard Normal Variate (SNV) and Savitzky–Golay smoothing of the spectral pattern with a window size of 5 and a second polynomial order were applied to the unfolded twelve samples as well as to the standard sample.

MCR-ALS software used was obtained from reference [4] and used under MATLAB environment (The Mathworks, Inc., USA)

PRELIMINAR RESULTS

Distribution concentration maps for each component were obtained, giving valuable visual information of the distribution of each component in the tablets. As an example, Figure 1 depicts three of the tablets. It can be observed how the API (lorazepam) is equally distributed in the surface. On the contrary, other excipients, like CMS and MCC were distributed forming small clusters. This may generate releasing or dissolution problems, changing the effectiveness of the drug.

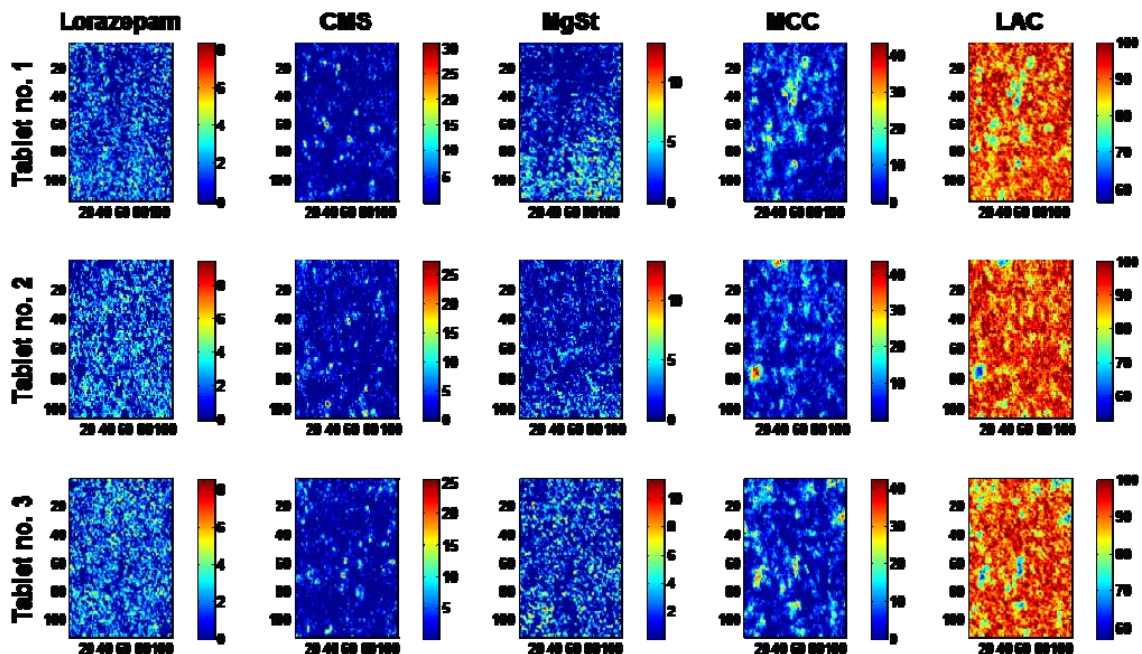


Fig 1. Concentration maps (in percentage) of all the components for three tablets.

The robustness and goodness of the models was assessed by the low and randomly distributed values of the residuals (results not shown) and the high correlation coefficient value between the spectral profiles obtained with MCR and their corresponding pure spectrum (Figure 2 and table 1).

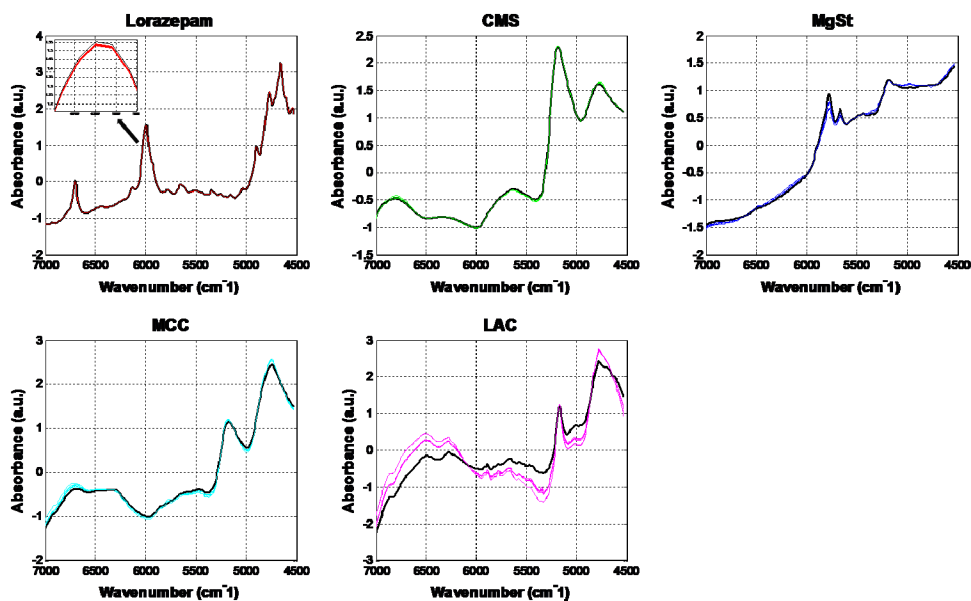


Fig 2. Pure spectrum (black) and obtained spectral profiles (coloured) for each compound of the tablets.



Table 1: Mean correlation coefficient and standard deviation of the obtained spectral profiles with MCR-ALS and the corresponding pure spectrum.

Component	Coefficient of correlation
Lorazepam	0.99997 ± 0.00002
Sodium Carboximethyl starch	0.99990 ± 0.00007
Magnesium stearate	0.99923 ± 0.00047
Microcrystalline cellulose	0.99871 ± 0.00088
Lactose monohydrate	0.94306 ± 0.02370

Figure 2 shows two interesting results: The abovementioned high correlation between MCR results and the pure spectra and, what is more interesting, some deviations in the spectral intensity in the obtained spectra of Lactose (LAC). LAC is the excipient which has the highest concentration in the tablet (around 90% of the composition). Therefore, any physical effect will be more evident in the lactose spectra. The differences observed between the obtained spectral profiles and the pure spectrum are due the different compression forces for each tablet.

FINAL COMMENTS AND FUTURE RESEARCH

This work demonstrates the usefulness of the combination of NIR-Hyperspectral imaging and MCR-ALS to assess the concentration of components in tablets and to obtain information about their distribution in the surface measured, even having components at a very low concentration. Future work encompasses several targets: the use of reference methods to compare the quantitative results and the stereological study of the distribution of the elements in the different concentration maps obtained.

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